Amendments to the Drawings:

The attached drawing sheet includes a change to Figure 4. This sheet replaces the original sheet Figure 4.

Attachment: Replacement Sheet

REMARKS

Reconsideration of the present application is respectfully requested in view of the above amendments and the following remarks. Claims 1-9 and 11-16 are pending; claims 1-9, 11-14, and 16 are currently under examination and claim 15 is withdrawn. Without acquiescence or prejudice, claims 1, 6, and 11 are amended to more particularly point out and distinctly claim certain embodiments of Applicants' invention, and claim 14 is canceled. No new matter has been added by the amendments. Support for the amendments can be found in the claims as filed (*see* claim 14), and in the specification as filed, for example, at page 26, line 25 to page 27, line 9. It should be noted that the amendment is made without prejudice to prosecution of any subject matter described in the instant application in a related divisional, continuation or continuation-in-part application.

REJECTIONS UNDER 35 U.S.C. §112, FIRST PARAGRAPH, ENABLEMENT, FIRST REJECTION

Claims 2-8 stand rejected under 35 U.S.C. §112, first paragraph, for alleged lack of enablement. The Examiner agrees that the specification enables methods of producing immunoglobulin (Ig) constant regions such as IgG, IgA, IgM, IgE, and IgD; ii) IgG1, IgG2, IgG3, and IgG4, as well as CH1, CH2, CH3, and CH4 or CL, but asserts that it does not enable the production of "combinations and hybrids thereof."

Applicants traverse this rejection and submit that persons skilled in the art could practice the full scope of the instant claims without undue experimentation, *i.e.,* using nothing more than routine experimentation.

It is well-established that the enablement requirement is satisfied when the disclosure contains sufficient information regarding the claimed subject matter, combined with the knowledge in the art, to enable one of ordinary skill in the art to make and use the claimed invention without undue experimentation. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). Applicants submit that the instant specification teaches a person skilled in the art how to make and use the presently claimed subject matter without undue experimentation, thus satisfying both the "how to make" and "how to use" arms of the enablement requirement.

First, the specification, in combination with the knowledge in the art, teaches persons skilled in the art how to "make," *i.e.,* obtain and identify, "combinations and hybrids" of Ig constant regions for use in the claimed method. Indeed, Applicants submit that the specification is replete with exemplary guidance on how to make the presently claimed Ig constant region constructs, which can be generated using nothing more than routine molecular biological techniques involving DNA cloning and PCR. For instance, the specification teaches by working examples the cloning of both dimeric and monomeric Ig constant region constructs (*e.g.*, Examples 3 and 4), and also teaches by working examples the cloning of a nucleotide sequence encoding a heavy chain constant region and a nucleotide sequence encoding a light chain constant region, as recited in claim 8 (*see, e.g.,* Example 3). In addition, Applicants submit herewith the Declaration of Sung Youb Jung and Jin Sun Kim ("the Declaration"), which, based on the working examples and guidance in the instant specification, illustrates the routine and successful cloning of a hybrid construct of the Ig constant regions from the hinge region and parts of the C_H2 region from IgG2, and from the C_H2 and C_H3 regions of IgG4 (*see* Item 5 of the Declaration; *see also* claim 6). Thus, as exemplified by the techniques in the specification and complemented by the routine nature of molecular cloning, Applicants submit that persons skilled in the art could readily and without undue experimentation obtain a variety of "combinations and hybrids" of Ig constant regions for use in the claimed method.

The specification, in combination with the knowledge in the art, also teaches persons skilled in the art how to *use* the presently claimed combinations and hybrids of Ig constant regions in the claimed methods. For instance, to complement the common knowledge in the art of such methods, the specification describes by working examples the expression and purification of the Ig constant regions produced by any of the molecular constructs of the invention (*see* Example 4). In addition, using nothing more than routine experimentation based on the guidance in the specification, the Declaration illustrates the successful soluble expression of a hybrid of an Ig constant region in *E. coli*, as noted above (*see* Item 6 of the Declaration). Hence, this evidence shows that methods of making (*e.g.*, cloning) and using (*e.g.*, expressing and purifying the protein in mass quantities) Ig constant region constructs, combinations, and hybrids thereof, may be routinely performed by persons skilled in the art by relying on nothing

more than routine experimentation, based on the guidance in the specification, as illustrated by the working examples therein as well as the Declaration.

Moreover, in combination with the above-guidance, it is respectfully submitted that persons skilled in the art can routinely identify or confirm whether their constructs of Ig constant region are useful by routinely screening the relevant functional characteristics of the polypeptides produced by the claimed process. In this regard, Applicants agree with the Examiner that the Ig constant regions produced by the claimed process should be functional and useful (*see* the Action, page 8), but submit that such utility is not necessarily related to the Ig constant region's effector functions in the context of an antibody. Instead, this utility may be related to its function as a *carrier* of a drug (*see, e.g.,* page 10, lines 13-15 of the specification). In this light, the references cited by the Examiner alleging that minor changes in an Fc region may alter its effector functions (*see* Lund *et al.*, *The Journal of Immunology* 157:4963-69, 1996) or may cause an antibody to lose its antigen affinity (*see* Lazar *et al.* WO 2003/074679) are inapposite to the instant claims, especially Lazar *et al.*, as the Ig constant regions of the instant methods have little or nothing to do with antibody affinity when used as a drug carrier. Rather, to confirm the utility of the Ig constant regions produced by the claimed methods, these molecules may be readily prepared as drug carriers, such as by conjugating them to a suitable drug, and tested for activity by performing routine screening on their pharmacokinetics (*e.g.,* increased half-life). Indeed, the instant specification describes this routine process by working examples (*see* Example 6). Applicants note that enablement is not precluded by the necessity for routine screening. *See In re Wands*, 858 F.2d 731 (Fed. Cir. 1988).

In view of the evidence on the state of the art and the presence of working examples, the predictability in the art also supports the enablement of the instant claims. In this regard, the Examiner's basis for rejecting the claims for lack of enablement appears to rely, at least in part, on the possibility that a single or a few amino acid substitutions in an Ig constant region may abrogate that polypeptides functionality (*see* the Action, page 9, second to last paragraph). The Examiner extrapolates from examples in the art that a single amino acid substitution in a particular protein has altered the protein's function, and then asserts that Applicants must therefore describe which constant domains may or may not be changed to meet

the requirements under 35 U.S.C. § 112, first paragraph. However, even assuming, *arguendo*, that the references cited by the Examiner stand for the general principle that single amino acid changes can alter the function of a protein (*see* Lund *et al.*), Applicants submit that the Examiner's reliance on such evidence does not fairly reflect the *predictability* in the art with regard to protein alterations and the expectations of their preserving any given function. Indeed, in general, the advanced state of the art at the time of filing demonstrates that to identify related polypeptide variants that *retain* their functional characteristics is *more predictable* than to identify those that lose their functional characteristics. This degree of predictability applies even in the absence of specific knowledge regarding which constant domains should or should not be changed to preserve any particular function (*see* the Action, page 7).

One highly illustrative example of the "predictability" of identifying *functional* polypeptide variants may be found in Wan *et al.* (*Mol. Endocrinol.* 17:2240-50 (2003), submitted herewith), which describes the process of screening for variants that retained function (binding to a monoclonal antibody) and variants that lost this function. In particular, Wan *et al.* prepared a library of 5200 random polypeptide variants, without consideration for tolerant or intolerant amino acids, and detected only 125 variants (less than 2.5%) that no longer specifically bound to a specific antibody. By quantifying the number of random variants that retain or lose the ability to bind a single, specific antibody, the teachings in Wan *et al.* reasonably reflect the "predictability" of the art with regard to the expectation that polypeptide variants (*e.g.,* hybrids) would retain the functional features of a reference polypeptide, such as the polypeptides of SEQ ID NOS. 21, 22, 23, 24, 25, 27, 29, 30, 34 and 35, and the Ig constant region sequences known in the art.

A more accurate reflection of the predictability in the general polypeptide art may also be found, for example, in passages of Bowie *et al.*, which teach that proteins are "surprisingly tolerant of amino acid substitutions" (*see* Bowie *et al.*, *Science* 247:1306 (1990), page 1306, right hand column, first full paragraph, submitted herewith). Further, according to textbook knowledge in the molecular biology art with respect to polypeptides, such as enzymes for example, "[in] fact, evidence now indicates that amino acid replacements in many parts of a polypeptide chain can occur without seriously modifying catalytic activity" *(see Molecular*

Biology of the Gene, page 227 (James D. Watson *et al.*, ed., The Benjamin/Cummings Publishing Co., (Menlo Park, CA) (4th ed. 1987)). Thus, even though these examples relate to amino acid substitutions as opposed to hybrids of polypeptide regions, the general understanding in the art is that structurally related polypeptides are more likely than not to retain the functional features of a given reference polypeptide. On this point, persons skilled in the art recognize that the sequence homology between IgG constant regions is very high, for example, over 90% homology in human, and over 88% homology between humans and certain monkeys, showing a high structural relationship among the various species of IgG constant regions. Given the evidence on the predictability in the art, as well as the high level of skill in the art, Applicants submit that persons skilled in the art can reasonably predict that such highly structurally related hybrids or combinations of the recited Ig constant regions will retain their relevant functionality as a drug carrier.

Further, and contrary to the Examiner's assertion, the quantity of experimentation required to practice the claimed subject matter is not undue. Although, as recognized by the Examiner, the claimed genus contains numerous variations (*see* the Action, page 8) or species, Applicants need not exemplify every species within a genus, and a person skilled in the art need not make every species to practice the claimed embodiments. The law is well settled that to satisfy the enablement requirement, an Applicant need not test every embodiment of an invention encompassed by a claim and need not describe a large number of examples, particularly when (as here) the level of skill in the art is high, and the teachings of the specification are ample. *See In re Strahilevitz*, 212 U.S.P.Q. 561, 563 (C.C.P.A. 1982) (finding that although the invention encompassed a large variety of compounds, a large number of examples would not be required because examples are not required to satisfy section 112, first paragraph). Moreover, even though a large number of polypeptide species may be made, Applicants are not required to list all operable embodiments of the invention and to exclude inoperable ones, if any. *See Atlas Powder Co. v. E. I. Dupont de Nemours & Co.,* 750 F.2d 1569, 1576 (Fed. Cir. 1984). In a more recent application of these still sound principles, Applicants further note that the test for enablement is not merely quantitative, and that a considerable amount of experimentation is permissible. *See Falko-Gunter Falkner v. Inglis*, 448

F.3d 1357, 1365 (Fed. Cir. 2006) (quoting the Board of Patent Appeals and Interferences, "the mere fact that the experimentation may have been *difficult* and *time consuming* does not mandate a conclusion that such experimentation would have been considered to be 'undue' in this art.")) (emphasis added).

Therefore, in view of the guidance provided in the specification, the presence of working examples, the predictability in the art, the high level of skill in the art, and the scope of the claims, which reasonably correlates with the working examples, the guidance provided in the specification, and the understanding and expectations in the art, Applicants submit that persons skilled in the art could practice the presently claimed subject matter without undue experimentation. As such, Applicants submit that the instant claims satisfy the enablement requirement under 35 U.S.C. § 112, first paragraph, and respectfully request withdrawal of this rejection.

REJECTIONS UNDER 35 U.S.C. §103

A. Claims 1 and 11 stand rejected under 35 U.S.C. §103(a) for alleged obviousness over Capon *et al.* (U.S. Application No. 2003/0104535) in view of Reilly *et al.* (U.S. Application No. 2005/0048572). The Examiner asserts that both Capon *et al.* and Reilly *et al.* teach methods of transforming prokaryotic cells to express an immunoglobulin (Ig) constant region having an *E. coli* derived signal peptide, and culturing the cells to express the Ig constant region for purification. The Examiner further asserts that Reilly *et al.* teach additional signal sequences, including the STII sequence of SEQ ID NO: 36. The Examiner then asserts that persons of ordinary skill in the art would have found it *prima facie* obvious to follow the teachings Capon *et al.* to include the *E. coli* derived signal peptide sequences of Reilly *et al.*, and would have had a reasonable expectation of success in practicing the presently claimed subject matter.

B. Claims 1 and 11 stand rejected under 35 U.S.C. §103(a) for alleged obviousness over Capon *et al.* in view of Reilly *et al.*, in further view of Kwon *et al.* (U.S. Patent No. 6,605,697). The Examiner asserts that Kwon *et al.* teach the STII peptides of SEQ ID NOs: 36-46, and then asserts that it would have been *prima facie* obvious to follow the teachings of

Capon *et al.* and Reilly *et al.* to include the *E. coli* derived signal peptide sequences of Kwon *et al.*

Applicants traverse each of the rejections in sections A and B above and submit that the instant claims satisfy the requirements of non-obviousness. To this end, Applicants submit that the Examiner has not established a *prima facie* case of obviousness with respect to the presently claimed subject matter. *See In re Mayne*, 104 F.3d 1339 (Fed. Cir. 1997) (The USPTO has the burden of showing a *prima facie* case of obviousness).

At a minimum, it must be demonstrated that the combined references teach or suggest all the claim features, and even assuming, *arguendo,* that the combination of references teach each claim feature, the Examiner must provide an explicit, apparent reason to combine these features in the fashion claimed by the Applicant with a reasonable expectation of success. *See KSR v. Teleflex, Inc.,* No. 04-1350 at 4, 14 (U.S. Apr. 30, 2007) ("A patent composed of several elements is not proved obvious merely by demonstrating that each element was, independently, known in the prior art"). Here, as previously made of record, the cited references fail to teach or suggest methods of producing an Ig constant region by transforming *E. coli* with a recombinant expression vector including a nucleotide sequence encoding a signal sequence isolated from *E. coli* and a nucleotide sequence encoding an Ig constant region, culturing a resulting transformant, and isolating and purifying the Ig constant region expressed by the transformant, wherein the signal sequence is a heat-stable enterotoxin II signal sequence, and wherein the Ig constant region is expressed in the cytoplasm in a water soluble form.

Applicants submit that the cited references *in combination* fail to teach or suggest each feature of the instant claims. For instance, Capon *et al.* do not teach an expression vector comprising a heat-stable enterotoxin II signal sequence, let alone do they teach such a vector that expresses an Ig constant region in the cytoplasm in a water soluble form, as recited in the instant claims. Reilly *et al.* do not remedy the defects of Capon *et al.*, as this reference, at best, describes a prokaryotic expression system for *complete antibodies* (*see* abstract), as opposed to the Ig constant regions of the present invention.

Moreover, Reilly *et al.* teach that their expression vector is used for the "*periplasmic secretion* of heavy and light chains" (*see, e.g.,* page 25, paragraph 216) (emphasis

added). In contrast, the instant claims recite an Ig constant region expressed from a vector comprising a heat-stable enterotoxin II signal sequence that is expressed in the *cytoplasm* in a *water-soluble form*. Similar to Reilly *et al.*, Kwon *et al.* merely describe additional signal sequences with enhanced secretion efficiency into the *periplasmic space* (*see, e.g.,* abstract and column 2, lines 34-38), and, thus, fail to remedy the deficiencies of Capon *et al.* and Reilly *et al.* In failing to teach or suggest each feature of the instant claims (*e.g.,* an Ig constant region/signal sequence polypeptide that is expressed in the *cytoplasm* in a *water-soluble form*), these references in combination fail to provide a requisite element of a *prima facie* case of obviousness.

In addition, the cited references fail to motivate persons of ordinary skill in the art at the time of filing to practice the presently claimed subject matter with a reasonable expectation of success. Here, the cited references provide no technical basis whatsoever to envisage the cytoplasmic, water-soluble protein expression of an Ig constant region, especially in view of the fact that Reilly *et al.* teach that antibody heavy or light chains fused to a signal sequence are secreted into the *periplasmic space*. Thus, even if persons of ordinary skill in the art combined the teachings of these references, such persons would not have arrived at the presently claimed methods, since none of these references teach or suggest fusions of Ig constant regions, nor do they teach or suggest methods that have been shown to yield cytoplasmic, and not periplasmic, water-soluble protein expression of Ig constant regions. Rather, a whole new line of experimentation would have been required to practice the instant methods, with nothing to suggest the successful practice thereof, as empirically demonstrated by Applicants. Since the cited references fail to teach or suggest each feature of the instant claims, and further fail to provide any reasonable expectation of practicing the presently claimed subject matter, then these references fail to establish a *prima facie* case of obviousness over the instant claims.

Further, the non-obviousness of the instant claims is supported by relevant secondary considerations, including evidence of improved properties and unexpected results. *See Graham v. John Deere Co.*, 383 U.S. 1, 17 (1996). For example, the instant methods offer improvements over conventional methods of secreting proteins into the *periplasmic space,* such as by allowing enhanced expression efficiency, among other advantages (*see, e.g.,* page 26, line

25 to page 28, line 13 of the specification). Also, according to the claimed methods, the specification provides experimental evidence supporting the improved and unexpected cytoplasmic, water-soluble expression of Ig constant regions (*see, e.g.*, Example 4; Figure 1; and Item 6 of the Declaration). Since none of these improved properties or unexpected results are found or suggested in the cited references, Applicants submit that this evidence provides relevant secondary indicia of non-obviousness, thereby supporting the patentability of these claims.

Therefore, in view of the failure of the cited references to teach or suggest each feature of the instant claims, and/or to provide any reasonable expectation of arriving at the claimed methods, as well as the improved properties and unexpected results shown by Applicants for such methods, Applicants submit that instant claims satisfy the requirements of non-obviousness under 35 U.S.C. § 103, and respectfully request withdrawal of this rejection.

OBJECTIONS TO THE DRAWINGS

The Examiner objected to the Replacement Sheets submitted by Applicants in the previous response. The Examiner asserts that Applicants are *required* to submit a marked-up copy of these Sheets under 37 C.F.R. § 1.121(d)(1).

Applicants respectfully disagree and submit that 37 C.F.R. § 1.121(d) does not necessarily *require* Applicants to submit a marked-up copy of the Replacement Sheets. Instead, this rule provides Applicants with the option of either submitting a marked-up copy, or explaining the changes in the Remarks section. Here, Applicants explained the rather simple change to Figure 4 in the Remarks section of the response to the Office Action of November 14, 2007 (*see* page 9 of Applicants' response of May 14, 2008). In particular, Applicants explained that the amendment to Figure 4 consists of labeling the Y-axis as "O.D. (450nm)," consistent with the description of that figure in Example 5 of the specification

Nonetheless, Applicants recognize that the Examiner may require Applicants to submit a marked-up "Annotated Sheet" of an amended figure under 37 C.F.R. § 1.121(d)(2). If that is the case here, then Applicants submit herewith both a Replacement Sheet for Figure 4 and a marked-up version of Figure 4 that includes annotations (in red) indicating the changes made to this figure. No new matter has been added by this amendment.

Therefore, Applicants submit that the Replacement Sheet for Figure 4 complies with the requirements of 37 C.F.R. § 1.121(d), and respectfully request both entry of this amendment, and withdrawal of this objection.

CLAIM OBJECTIONS

The Examiner objected to claim 11 for depending from canceled claim 10. Applicants thank the Examiner for pointing out this inadvertent error and note that claim 11 has been amended to depend from claim 1. Thus, Applicants kindly request withdrawal of this objection.

REJECTIONS UNDER 35 U.S.C. §112, FIRST PARAGRAPH, ENABLEMENT, SECOND REJECTION

Claims 1-9, 11-12, 14, and 16 stand rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. Essentially, the Examiner agrees that the specification enables the practice of the claimed methods in *E. coli*, but asserts that it does not enable the practice of such methods in any prokaryotic cell.

Applicants traverse this rejection and submit that persons skilled in the art can practice the presently claimed methods in any prokaryotic organism without undue experimentation. Nonetheless, without acquiescence or prejudice to pursuing the encompassed subject matter in a related application, claim 1 as amended herewith relates, in pertinent part, to methods of producing an Ig constant region in *E. coli*. Support for this amendment is provided in the instant specification and claims as filed, including, *e.g.*, original claim 14. Applicants believe that this amendment obviates the Examiner's enablement rejection of the instant claims.

Therefore, Applicants submit that the instant claims satisfy the enablement requirement under 35 U.S.C. § 112, first paragraph, and kindly request withdrawal of this rejection.

Applicants believe that all of the claims in the application are allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Respectfully submitted,

SEED Intellectual Property Law Group PLLC

/Carol D. Laherty/
Carol D. Laherty, Ph.D.
Registration No. 51,909

WTC:CDL:jto

Enclosure:
Rule 132 Declaration of Sung Youb Jung and Jin Sun Kim
1 Replacement Sheet (Figure 4)
1 Annotated Sheet (Figure 4)
Wan *et al.* (*Mol. Endocrinol.* 17:2240-50 (2003)
Bowie *et al.*, *Science* 247:1306 (1990)

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